British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2019) **85** 277–280 277

LETTER TO THE EDITOR

Once-daily darunavir/ritonavir 400/100 mg in triple therapy: efficacy and penetration in seminal compartment in ANRS-165 DARULIGHT study

Correspondence Dr Minh P. Lê, AP-HP, Hôpital Bichat-Claude Bernard, Laboratoire de Pharmacologie-Toxicologie, 46 rue Henri Huchard, 75018 Paris, France. Tel.: +33 1 40 25 84 54; Fax: +33 1 40 25 88 12; E-mail: minh.le@aphp.fr

Received 12 June 2018; **Revised** 28 September 2018; **Accepted** 12 October 2018

Minh P. Lê[1,2], Marie-Laure Chaix[3], François Raffi[4], Sylvie Chevret[5], Sébastien Gallien[6], Christine Katlama[7], Pierre Delobel[8], Yazdan Yazdanpanah[1,9], Juliette Saillard[10], Jean-Michel Molina[11], Gilles Peytavin[1,2] and the ANRS-165 DARULIGHT study group*

[1]IAME, UMR 1137, Université Paris Diderot, Sorbonne Paris Cité and INSERM, Paris, France, [2]AP-HP, Hôpital Bichat-Claude Bernard, Laboratoire de Pharmacologie-Toxicologie, Paris, France, [3]AP-HP, Hôpital Saint Louis, Laboratoire de Virologie, INSERM U941, Université Denis Diderot Paris VII, F-75010 Paris, France, [4]Department of Infectious Diseases, Hotel-Dieu Hospital, INSERM CIC 1413, Nantes University Hospital, Nantes, France, [5]AP-HP, Hôpital Saint Louis, SBIM-URC, Paris, France, [6]AP-HP, CHU Henri Mondor, Service d'Immunologie Clinique et Maladies Infectieuses, Créteil, France, [7]AP-HP, Hôpital Pitié-Salpêtrière, Service de Maladies Infectieuses et Tropicales, Paris, France, [8]CHU de Toulouse, Service de Maladies Infectieuses et Tropicales, Toulouse, France, [9]AP-HP, Hôpital Bichat-Claude Bernard, Service de Maladies Infectieuses et Tropicales, Paris, France, [10]France Recherche Nord & Sud SIDA-HIV Hépatites (ANRS), Paris, France, and [11]AP-HP, Hôpital Saint Louis, Service de Maladies Infectieuses et Tropicales, INSERM U941, Université Denis Diderot Paris VII, F-75010 Paris, France

*Members are listed in Appendix.

Keywords darunavir, dose reduction, seminal and blood plasma, unbound total

A key concern for reduced-dose antiretroviral regimens in maintenance strategies in HIV-infected patients is virological efficacy, as assessed by the suppression of HIV-RNA in blood and reservoirs, such as the genital tract. The risk of minority variants emerging in reservoirs with different antiretroviral drug penetrations and immune pressures is also a matter of concern [1–4]. Thus, antiviral activity and drug penetration into deep compartments must be considered in reduced-dose strategies.

The ANRS-165 DARULIGHT trial (NCT#02384967) was a prospective, multicentre, phase II open-label trial assessing whether low-dose **ritonavir**-boosted darunavir (DRV/r 400/100 mg once-daily) could, in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), maintain virological suppression in plasma (≤50 copies ml^{-1}), in 100 HIV-1-infected patients receiving a standard regimen of DRV/r (800/100 mg once-daily) + 2NRTIs. The treatment success rate at week 48 was 91.6% [5], and an intensive steady-state pharmacokinetic analysis on 15 patients [median age: 42 years (41–47)], from weeks 0 to 12, demonstrated no significant decrease in total DRV blood plasma exposure despite a 50% decrease in the daily dose of DRV (AUC_{0-24} = 65 563 ng·hr ml^{-1} *vs.* 52 518 ng·hr ml^{-1}; P = 0.25) [6]. This substudy aimed to assess the antiviral activity and penetration into the seminal compartment of DRV/r (400/100 mg once-daily), in a maintenance strategy.

DOI:10.1111/bcp.13796

Table 1

HIV-1 RNA (VL, copies ml^{-1}) and antiretroviral trough concentrations (C_{min}, ng ml^{-1}, n = 13 patients) in blood and seminal plasma at week 0 (W0) and W12

		Blood plasma								Seminal plasma						
ID		VL	Total DRV C_{min}	Unbound DRV C_{min}	Total RTV C_{min}	Total FTC C_{min}	Total TFV C_{min}	Total ABC C_{min}	Total 3TC C_{min}	VL	Total DRV C_{min}	Unbound DRV C_{min}	Total FTC C_{min}	Total TFV C_{min}	Total ABC C_{min}	Total 3TC C_{min}
1	W0	<50	1862	95	51	-	-	<5	48	<100	85	66	-	-	<5	335
	W12	<50	876	60	57	-	-	<5	48	-	-	-	-	-	-	-
2	W0	<50	2123	149	51	65	84	-	-	202	186	170	743	449	-	-
	W12	<50	1635	92	38	66	65	-	-	<50	120	88	680	269	-	-
3	W0	<50	3026	160	33	54	57	-	-	<50	504	204	240	115	-	-
	W12	<50	2409	110	64	71	43	-	-	<100	134	87	396	157	-	-
4	W0	<50	1583	80	57	93	90	-	-	<50	229	153	569	668	-	-
	W12	<50	792	46	78	159	104	-	-	<50	87	56	978	996	-	-
5	W0	<50	1019	81	424	76	52	-	-	<100	105	94	356	54	-	-
	W12	<50	775	37	42	78	52	-	-	<200	-	-	-	-	-	-
6	W0	<50	824	65	43	98	26	-	-	<50	310	270	3592	176	-	-
	W12	<50	344	31	47	83	26	-	-	<50	57	38	1007	43	-	-
7	W0	<50	1025	60	22	83	43	-	-	<50	56	46	304	98	-	-
	W12	<50	786	37	35	80	49	-	-	<50	61	37	357	43	-	-
8	W0	<50	400	27	26	41	35	-	-	928	28	23	251	43	-	-
	W12	<50	657	50	54	37	22	-	-	105	62	47	243	14	-	-
9	W0	<50	638	58	44	60	35	-	-	<100	-	-	-	-	-	-
	W12	<50	856	54	48	73	44	-	-	<100	-	-	-	-	-	-
10	W0	<50	756	59	22	83	61	-	-	<500	107	66	1015	896	-	-
	W12	<50	2726	156	92	444	113	-	-	<50	123	73	1061	412	-	-
11	W0	<50	1180	88	26	-	-	18	39	-	-	-	-	-	-	-
	W12	<50	415	24	16	-	-	<5	35	1005	-	-	-	-	-	-
12	W0	<50	897	61	33	-	-	<5	42	<300	85	56	-	-	16	2834
	W12	<50	324	16	46	-	-	<5	55	<50	60	32	-	-	13	4973
13	W0	<50	793	48	52	62	69	-	-	<100	123	76	477	161	-	-
	W12	<50	1940	87	106	70	70	-	-	<500	110	83	569	216	-	-

3TC, lamivudine; ABC, abacavir; DRV, darunavir; FTC, emtricitabine; TFV, tenofovir

Patients presenting detectable seminal viral load are highlighted in grey. Unbound blood plasma and both total and unbound seminal concentrations of ritonavir were all below the limit of quantification. Semen samples were missing or insufficient for patient #1W12 and patient #11W0/12

Written informed consent for the pharmacokinetic substudy was obtained in addition to informed consent to participate in the main study (Eudract CT number: 2014-001505-40).

Blood samples were collected 24 hr after the last drug intake (C_{min}). Semen samples were collected, by self-masturbation after at least 3 days of sexual abstinence, 24 hr after the last dose, for 13 of the 15 patients. Blood and seminal plasma were stored at −80°C. Blood and seminal plasma concentrations of total (DRV, RTV and NRTIs) and unbound (DRV only) drugs were determined by UPLC-MS/MS (Waters Acquity UPLC-TQD, Milford, MA, USA) [7]. Binding to plasma proteins was assessed in an ultrafiltration assay (Centrifree; Millipore, Molsheim, France). All respective coefficients of variation were <15%, and the limits of quantification were 5 ng ml^{-1} for darunavir and NRTIs and 10 ng ml^{-1} for ritonavir. The blood plasma C_{min} of darunavir was considered adequate, based on a 10-fold *in vitro* protein binding-corrected median effective concentration required to induce 50% virological response (EC_{50}) of 550 ng ml^{-1} [8]. HIV-1 RNA was quantified in blood and seminal plasma with the COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test v2.0 (Roche Diagnostics, Meylan, France). The thresholds used were 50 copies ml^{-1} for blood plasma and up to 500 copies ml^{-1} for seminal plasma, according to the dilution used to prevent PCR inhibition. The results are presented as the median (interquartile range) at W0 (DRV/r 800/100 mg once-daily) and W12 (DRV/r 400/100 mg once-daily). Statistical comparisons were performed with Wilcoxon tests on paired W0–W12 data ($P < 0.05$).

Blood plasma was available for all 15 patients, and seminal plasma was available for 13 patients, with two missing samples at W0 and four at W12 (Table 1). No difference in total or unbound DRV C_{min} in blood or seminal plasma could be demonstrated between W0 and W12 (P = 0.380 and 0.157, respectively). The ratio of seminal plasma total/blood plasma unbound DRV C_{min} was 1.39 (1.14–2.71). Furthermore, blood and seminal plasma total DRV C_{min} were correlated (r = 0.718) and consistent with previous data [9, 10]. These results suggest that the unbound fraction of DRV well penetrated the semen and that the seminal concentration of DRV can be predicted from blood plasma total DRV C_{min}. A plasma HIV-1 RNA <50 copies ml^{-1} was maintained in all patients until week 12. However, three patients (Table 1) presented detectable seminal plasma HIV-1 RNA (202, 928 and 105; 1005 copies ml^{-1}, respectively) with an inadequate blood and/or seminal plasma C_{min} of darunavir (except for one patient) probably due to adherence issue. Also, all three patients presented detectable (or not assessed) HIV-1 RNA in seminal plasma at W0, suggesting no probable effect of the reduced-dose strategy on the HIV shedding in semen. As in a previous study describing the penetration of DRV into cerebrospinal fluid with a regimen including a weaker dose reduction for DRV (600/100 mg once-daily) [11], we detected viral replication in the deep compartment in patients with low DRV blood plasma exposure. The total C_{min} of NRTIs did not differ significantly between W0 and W12, and these drugs accumulated in seminal plasma with overall median seminal plasma concentrations consistent with previous data [12, 13]: emtricitabine 569 ng ml^{-1} (356–1000), tenofovir 169 ng ml^{-1} (65–440), abacavir 13 ng ml^{-1} (5–16) and lamivudine 2834 ng ml^{-1} (335–4973).

This study is the first to assess the penetration of DRV into semen in patients treated with a reduced-dose regimen. Even if residual HIV shedding in semen is probably intermittent and multifactorial, the impact of the reduced dose of DRV/r in maintenance on HIV seminal shedding was difficult to assess. Also, the prevalence of detectable HIV-RNA in semen seemed close to that of the standard triple therapy and might probably be more linked to adherence difficulties.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [14].

Competing Interests

M.P.L. has received travel grants from Bristol-Myers-Squibb and Janssen. M.-L.C. Chaix has received travel grants from Gilead Sciences, Janssen, Merck and ViiV Healthcare. F.R. has received research funding or honoraria from or acted as a consultant for Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, MSD and ViiV Healthcare. C.K. has served on advisory boards for Merck Sharp & Dohme (MSD) and Janssen and has been a clinical investigator for MSD, Janssen and ViiV Healthcare. P.D. has received travel grants from Bristol Myers Squibb, Janssen and Merck, and his institution has received grants from ViiV Healthcare. J.-M.M. has participated in advisory boards for Gilead, Merck, Janssen, ViiV, Bristol Myers Squibb and Teva, and his institution has received grants from Merck and Gilead. G.P. has received travel grants, consultancy fees, honoraria or study grants from various pharmaceutical companies, including Bristol-Myers-Squibb, Gilead Sciences, Janssen, Merck and ViiV Healthcare. The other authors have no competing interests to declare.

We thank all the participating patients and the study nurses at the clinical sites. This study was sponsored by the French National Agency for Research on AIDS and Viral Hepatitis (ANRS).

Appendix

The ANRS-165 DARULIGHT study team included the following investigators and co-investigators not listed among the authors: Dr. D. Ponscarme, Dr. C. Lascoux (AP-HP, Hôpital Saint-Louis, Paris); Prof. P. M. Girard (AP-HP, Hôpital Saint-Antoine, Paris); Dr. A. Rami (AP-HP, Hôpital Lariboisière, Paris); Prof. Y. Yazdanpanah (AP-HP, GH Bichat – Claude Bernard, Paris); Dr. A. Simon (AP-HP, GH Pitié Salpétrière, Internal Medicine, Paris); Dr. R. Tubiana (AP-HP, GH Pitié Salpétrière, Infectious Diseases, Paris); Dr. C. Duvivier (AP-HP, Hôpital Pasteur-Necker, Paris); Dr. V. Jeantils (AP-HP, Hôpital Jean Verdier, Bondy); Dr. D. Loreillard (Hôpital de Nimes); Dr. I. Poizot-Martin (AP-HM, Hôpital Ste Marguerite, Marseille); Prof. L. Bernard, Dr. G. Gras (CHU de Tours); Dr. C. Allavena, Dr. E. Billaud, Dr. S. Bouchez, Dr. N. Hall, Dr. V. Reliquet, Prof. F. Raffi (CHU de Nantes). Members of the DSMB included: Dr. P. De Truchis, I. Charreau, Dr. L. Bocquet, Prof. V. Lemoing and G. Point. Members of

the scientific committee included: Prof. J. M. Molina, Prof. S. Chevret, E. M. El Abassi, Dr. S. Gallien, Prof. P. Tattevin, Dr. G. Gras, Dr. M. L. Chaix, Dr. G. Peytavin, J. Saillard, S. Couffin-Cadiergues, I. Madelaine, A. Diallo and S. Gibowski.

References

1 Anderson JA, Ping L-H, Dibben O, Jabara CB, Arney L, Kincer L, *et al*. HIV-1 populations in semen arise through multiple mechanisms. PLoS Pathog 2010; 6: e1001053.

2 Lafeuillade A, Solas C, Halfon P, Chadapaud S, Hittinger G, Lacarelle B. Differences in the detection of three HIV-1 protease inhibitors in non-blood compartments: clinical correlations. HIV Clin Trials 2002; 3: 27–35.

3 Lafeuillade A, Solas C, Chadapaud S, Hittinger G, Poggi C, Lacarelle B. HIV-1 RNA levels, resistance, and drug diffusion in semen versus blood in patients receiving a lopinavir-containing regimen. J Acquir Immune Defic Syndr 2003; 32: 462–4.

4 Lê MP, Belarbi L, Chaix M-L, Dulioust E, Mahjoub N, Salmon D, *et al*. Penetration and antiviral efficacy of total and unbound maraviroc, raltegravir and rilpivirine in both female and male genital fluids from HIV-positive patients receiving regimens containing these antiretrovirals. J Antimicrob Chemother 2017; 72: 3167–71.

5 Molina J-M, Gallien S, Chaix M-L, El Abbassi EM, Madelaine I, Katlama C, *et al*. Low-dose ritonavir-boosted darunavir in virologically suppressed HIV-1-infected adults: an open-label trial (ANRS 165 Darulight). J Antimicrob Chemother 2018; 73: 2129–36.

6 Lê MP, Chaix M-L, Chevret S, Bertrand J, Raffi F, Gallien S, *et al*. Pharmacokinetic modelling of darunavir/ritonavir dose reduction (800/100 to 400/100 mg once daily) in a darunavir/ritonavir-containing regimen in virologically suppressed HIV-infected patients: ANRS 165 DARULIGHT sub-study. J Antimicrob Chemother 2018; 73: 2120–8.

7 Jung BH, Rezk NL, Bridges AS, Corbett AH, Kashuba ADM. Simultaneous determination of 17 antiretroviral drugs in human plasma for quantitative analysis with liquid chromatography–tandem mass spectrometry. Biomed Chromatogr BMC 2007; 21: 1095–104.

8 Ortiz R, DeJesus E, Khanlou H, Voronin E, van Lunzen J, Andrade-Villanueva J, *et al*. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. AIDS 2008; 22: 1389–97.

9 Lambert-Niclot S, Peytavin G, Duvivier C, Poirot C, Algarte-Genin M, Pakianather S, *et al*. Low frequency of intermittent HIV-1 semen excretion in patients treated with darunavir-ritonavir at 600/100 milligrams twice a day plus two nucleoside reverse transcriptase inhibitors or monotherapy. Antimicrob Agents Chemother 2010; 54: 4910–3.

10 Lambert-Niclot S, Poirot C, Tubiana R, Houssaini A, Soulié C, Dominguez S, *et al*. Effect of antiretroviral drugs on the quality of semen. J Med Virol 2011; 83: 1391–4.

11 Di Yacovo MS, Moltó J, Ferrer E, Curran A, Else L, Gisslén M, *et al*. Antiviral activity and CSF concentrations of 600/100 mg of darunavir/ritonavir once daily in HIV-1 patients with plasma viral suppression. J Antimicrob Chemother 2015; 70: 1513–6.

12 Valade E, Tréluyer J-M, Illamola SM, Bouazza N, Foissac F, De Sousa Mendes M, *et al*. Emtricitabine seminal plasma and blood plasma population pharmacokinetics in HIV-infected men in the EVARIST ANRS-EP 49 study. Antimicrob Agents Chemother 2015; 59: 6800–6.

13 Valade E, Bouazza N, Lui G, Illamola SM, Benaboud S, Treluyer J-M, *et al*. Population pharmacokinetic modeling of tenofovir in the genital tract of male HIV-infected patients. Antimicrob Agents Chemother 2017; 61. https://doi.org/10.1128/AAC.02062-16.

14 Harding SD, Sharman JL, Faccenda E, Southan C, Pawson AJ, Ireland S, *et al*. The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. Nucl Acids Res 2018; 46: D1091–106.